REMARKS

The Office Action

Claims 102 and 104-109 are pending in this application. Claims 102 and 104-109 are rejected under 35 U.S.C. § 101 for lack of utility. Claims 102 and 104-109 are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement based on a lack of utility. Claims 104-109 are rejected under 35 U.S.C. § 112, first paragraph, for lack of written description, and claims 105, 107, and 108 are rejected under 35 U.S.C. § 112, second paragraph, for indefiniteness. Finally, claims 102 and 104-109 are variously rejected under 35 U.S.C. §§ 102(b) or 102(e) for lack of novelty over Konishi (U.S. Patent No. 4,461,724; hereinafter "Konishi"), Schmid (U.S. Patent No. 5,919,895; hereinafter "Schmid"), Penning et al. (J. Biol. Chem. 257:12589-12593, 1982; hereinafter "Penning"), Strominger et al. (J. Am. Chem. Soc. 81:3803-3804, 1959; "Strominger"), and Wang et al. (U.S. Patent No. 6,608,026; hereinafter "Wang"). By this reply, Applicants amend claims 102, 104, and 106-109, cancel claim 105, and address each of the rejections.

Support for the Amendment

Claims 102, 104, and 106-108 have been amended to remove reference to "fragments" of Factor XI and to harmonize the claim language. Claim 109 has been amended to more clearly recite the claimed subject matter. Support for new claim 109 is found in prior claim 109. No new matter is added by the amendment.

Objection to the Information Disclosure Statement

The Examiner states that "[t]he information disclosure statement filed on March 31, 2006 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609...[and that the information disclosure statement] has been placed in the application file, but the information referred to therein has not been considered as to the merits" (Office Action, p. 2; emphasis in original omitted). In response, Applicants resubmit the information disclosure statement herewith and additionally include a Form PTO-1449 listing the information submitted. Specifically, the Form PTO-1449 lists the information as "Information," provides a column with a blank space next to the entry for the Examiner's initials, and includes a heading that clearly indicates that the list is an information disclosure statement. Applicants note that the submitted information falls under the category of "all other information" specified in 37 C.F.R. § 1.98. Applicants believe that the information disclosure statement fully complies with the requirements set forth in 37 C.F.R. §§ 1.97 and 1.98, and respectfully request that the Examiner consider the information disclosure statement.

Rejections under 35 U.S.C. §§ 101 and 112, first paragraph

The Examiner rejects claims 102 and 104-109, stating that "the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility...The instantly claimed Factor XI proteins and fragments are research tools for designing and determining inhibitors of Factor XI (e.g., Abstract, throughout)" (Office Action, p. 3). In addition, the Examiner states that "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility..., one skilled in the art

clearly would not know how to use the claimed invention" (Office Action, p. 5). In support of this conclusion, the Examiner points to portions of the present specification that disclose embodiments of the present invention directed to the design of high affinity inhibitors of Factor XI ("In desirable embodiments, mutation(s) [in Factor XI] allow crystallization or increase resolution of the corresponding three-dimensional structure of the mutant protein compared to the structure of Factor XI without the mutation(s)"; see page 42, lines 4-8). Applicants respectfully traverse this rejection.

Standards for Satisfying the Utility Requirement

The Utility Examination Guidelines (66 CFR 1092-1099) and Revised Interim Utility Guidelines Training Materials outline the criteria for determining the utility of an invention. The utility of an invention must be specific and substantial or well-established. In defining the metes and bounds of a specific utility, the Revised Interim Utility Guidelines Training Materials require that:

> a utility [be] specific to the subject matter claimed. This contrasts with a general utility that would be applicable to the broad class of the invention ... A general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed (paragraph bridging pages 5 and 6; emphasis added).

By implication, therefore, the specific utility of a particular protein may be established by the disclosure of a specific disease or condition with which it is associated.

Likewise, a substantial utility is established by a "real world" context of use, such as the identification of a material which can be used to identify a therapeutic for treating or preventing a particular disease or condition. Specifically, the Revised Interim Utility Guidelines state:

> both a therapeutic method of treating a known or newly discovered disease and an assay method for identifying compounds that themselves have a "substantial utility" define a "real world" context of use. An assay that measures the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease condition would also define a "real world" context of use in identifying potential candidates for preventive measures or further monitoring (page 6; emphasis added).

Thus, a component of an assay method for identifying candidate compounds which may be used for treating a specific disease itself has substantial utility.

Alternatively, the utility requirement of 35 U.S.C. § 101 can also be satisfied by identifying a well established utility, which is defined in the Revised Interim Utility Guidelines Training Materials as:

> A specific, substantial, and credible utility which is well known, immediately apparent, or implied by the specification's disclosure of the properties of a material, alone or taken with the knowledge of one skilled in the art (page 7; emphasis added).

Of course, in evaluating the utility of the invention, the credibility of the disclosure must be assessed. Credibility must be viewed from the perspective of a person of ordinary skill in the art and should be based on the totality of the evidence (specification and prior art) and reasoning provided.

The Federal Circuit in *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995), has articulated the standard to be applied by the PTO in any challenge to an assertion of utility. In this case, the court stated:

> the PTO has the initial burden of challenging a presumptively correct assertion of utility in the disclosure. [citation omitted]. Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility (page 1566; emphasis added).

The Examiner has failed to carry this burden. As is discussed below, Applicants'

specification asserts the specific and substantial utility of using mutant Factor XI proteins to identify inhibitors of full-length Factor XI, which can then be used to treat or prevent a variety of medical disorders where anticoagulant therapy is indicated, e.g., in the treatment or prevention of thrombotic conditions, such as coronary artery and cerebro- and peripheral vascular disease, associated with Factor XI activity (see page 173, lines 14-19, of the specification). Further, the Examiner has presented no credible evidence that would cause a person of ordinary skill to doubt the asserted utility of the present invention. On these bases, this rejection of claims 102, 104, and 106-109 for lack of utility under 35 U.S.C. § 101 and for lack of enablement under 35 U.S.C. § 112, first paragraph, should be withdrawn.

Specific Utility of Mutant Factor XI Proteins

The present invention is based on Applicants' discovery that purified Factor XI proteins that include amino acids 370-607 of SEQ ID NO: 15 and one or more of the mutations recited in present claims 102, 104, and 106-108, or, in the case of claim 109, a purified Factor XI protein that includes amino acids 370-605 (i.e., a Factor XI protein that lacks the C-terminal alanine and valine residues at positions 606 and 607 of the mature human Factor XI polypeptide sequence set forth in SEQ ID NO: 15) can be used to identify inhibitors of full-length Factor XI activity. The inhibitors identified using the mutant Factor XI proteins of present claims 102, 104, and 106-109 can be used in a variety of real world applications, including as therapeutics for the treatment or prevention of thrombotic conditions, as is discussed above. This aspect of Applicants' invention is discussed in detail in the specification (see, e.g., page 30, line 6, through page

35, line 17, page 41, line 5, through page 42, line 10, page 73, line 15, through page 76, line 26, page 87, line 25, through page 89, line 18, page 92, line 12, through page 95, line 26, and page 185, line 2, through page 186, line 22). Thus, Applicants' specification identifies specific uses of the mutant Factor XI proteins of the present claims that are the basis for Applicants' asserted utility.

Inhibitors Identified using Mutant Factor XI Proteins have Therapeutic Utility for the Treatment of Thrombotic Conditions

The disclosed ability of mutant Factor XI proteins to facilitate the identification of compounds capable of inhibiting full-length Factor XI strongly supports not only a specific utility for the presently claimed mutant Factor XI protein, but also a substantial "real world" utility based on the fact that the Factor XI inhibitors identified using the claimed mutant Factor XI proteins can be used as therapeutics for treating or preventing thrombotic conditions in a subject. As stated on page 2, lines 14-24, of the specification:

> The invention...provides three-dimensional structures of Factor XIa and methods for designing or selecting additional Factor XIa inhibitors using these structures. Desirably, these compounds have certain structural, physical, and spatial characteristics that enable the compounds to interact with specific residues of the active site of Factor XIa. (Page 3, lines 14-18.)
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> ****
>
> In addition to their use in anticoagulant therapy, Factor XIa inhibitors are useful in the treatment and prevention of other diseases in which the generation of thrombin has been implicated as playing a physiologic role. For example, thrombin has been implicated in contributing to the morbidity and mortality of chronic and degenerative diseases such as cancer, arthritis, atherosclerosis, and Alzheimer's disease by its ability to regulate many different cell types through specific cleavage and activation of a cell surface thrombin receptor, mitogenic effects, diverse cellular functions such as cell proliferation, for example, abnormal proliferation of vascular cells resulting in restenosis or angiogenesis, release of PDGF, and

> DNA synthesis. Inhibition of Factor XIa effectively blocks thrombin generation and therefore neutralizes any physiologic effects of thrombin on various cell types. The representative indications discussed above include some, but not all, of the potential clinical situations amenable to treatment with a Factor XIa inhibitor. (Page 30, lines 6-19.)

From this disclosure, a skilled artisan would clearly understand that the claimed mutant Factor XI proteins are useful for identifying inhibitors that can be used in "real world" applications (e.g., in the treatment of thrombotic conditions). In fact, using the methods disclosed in the present specification, Applicants have identified several compounds that inhibits Factor XI, at least one of which, compound 22, has been shown to suppress thrombus formation when tested *in vivo* in an accepted animal model of the relevant disease condition (see page 185, line 2, through page 186, line 22). Applicants note that the asserted disease associations are neither general in nature, nor are they inconsistent with what one skilled in the art would expect for the specific disease involvement of Factor XI inhibitors identified using the mutant Factor XI proteins of present claims 102, 104, and 106-109. Thus, Applicants have asserted a specific, substantial, and credible utility with a "real world" context for the mutant Factor XI proteins of present claims 102, 104, and 106-109.

Credible, Specific, and Substantial Utilities Have Been Asserted

The analysis to be carried out in making a rejection under 35 U.S.C. § 101, and in making a related rejection under 35 U.S.C. § 112, first paragraph, must include a determination of whether an assertion of utility has been made in an Applicants' specification and, if so, whether that asserted utility is credible (i.e., whether the assertion of utility is believable to a person of ordinary skill in the art based on the totality of

evidence and reasoning provided; M.P.E.P. § 2107.01-III(B)).

In the present case, Applicants have asserted at least one utility, discussed above, which is sufficient to satisfy the requirements of 35 U.S.C. §§ 101 and 112. Applicants submit that, absent data to the contrary, it is credible that the mutant Factor XI proteins of present claims 102, 104, and 106-109 can be used to identify inhibitors of Factor XI, which themselves can be used to treat or prevent thrombotic conditions in a subject. The Examiner has not stated that this utility lacks credibility, nor has any evidence been provided to dispute Applicants' assertion that this utility is credible, as the Guidelines require. In particular, the Guidelines state that the Office

> must treat as true any statement of fact made by the Applicant in relation to the asserted utility, unless countervailing evidence can be provided that shows that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of such a statement... [I]t is improper to disregard the opinion [of a qualified expert] solely because of a disagreement over the significance or meaning of the facts offered. (M.P.E.P. § 2107, emphasis added)

To be properly rejected under § 101, the Guidelines set forth that a case must represent one of those rare instances that meets the stringent criterion of being "totally incapable of achieving a useful result," *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555 (Fed. Cir. 1992), as cited in the Legal Analysis accompanying the Utility Examination Guidelines (M.P.E.P. § 2107.01-II). The only instances in which the federal courts have found a lack of patentable utility were where, "based upon the factual record of the case, it was clear that the invention could and did not work as the inventor claimed it did" (M.P.E.P. § 2107.01-II, emphasis added). These rare cases have been ones in which the applicant either (a) failed to disclose any utility for the invention, or (b) asserted a utility that could be true only "if it violated scientific principle, such as the

second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art" (M.P.E.P. § 2107.02-III(B)).

Procedurally, the M.P.E.P. makes clear that the burden is on the Examiner to provide a detailed, reasoned explanation for the rejection that is supported, if possible, by documentary evidence indicating why the asserted utility is more likely than not "incredible." "An applicant's assertion of utility creates a presumption of utility" (M.P.E.P. § 2107.01-III(A)); "Where an applicant has specifically asserted that an invention has a particular utility, that assertion cannot simply be dismissed by Office personnel as being 'wrong,' even when there may be reason to believe that the assertion is not entirely accurate" (M.P.E.P. § 2107.01-III(B)). Conversely, if the Examiner determines that the claimed invention has a credible utility, neither a 35 U.S.C. § 101 nor a related 35 U.S.C. § 112 rejection may be applied (or, upon rebuttal of the Examiner's position, both rejections must be simultaneously withdrawn).

In the present case, Applicants assert a specific and substantial utility in the specification that is, on its face, credible. Applicants assert that the present invention provides mutant Factor XI proteins that can be used to identify inhibitors of Factor XI that can be used to treat or prevent thrombotic conditions. In fact, Applicants have demonstrated that at least one of the identified inhibitors, compound 22, suppresses thrombus formation *in vivo* when tested in an acceptable animal model of the disease condition (see pages 185-186 of the specification). The benefit of the mutant Factor XI proteins, in view of their ability to identify Factor XI inhibitors useful for treating or preventing thrombotic conditions, would be acknowledged by one skilled in the art. No evidence has been made of record to dispute this utility, and on this basis alone the

rejection should be withdrawn.

Mutant Factor XI Proteins do not Fall into any of the Categories Deemed to Lack Substantial Utility

The Examiner states:

> In the instant case, the utility is a "general utility", as the MPEP states that the following categories are not substantial utilities: (A) Basic research such as studying the following categories of the claimed product itself or the mechanisms in which the material is involved; (B) A method of treating an unspecified disease or condition; (C) A method of assaying for or identifying a material that itself has no specific and/or substantial, and credible utility; and (E) A claim to an intermediate product for use in making a final product that has no specific, substantial and credible utility. MPEP § 2107.01(I). (Office Action, p. 4.)

As is clear from the discussion above, the mutant Factor XI proteins of present claims 102, 104, and 106-109 provide more than simply a "general utility"; for the reasons discussed above the claimed proteins provide both a specific and substantial utility and a credible utility.

Furthermore, the claimed mutant Factor XI proteins do not fall within any of the categories listed above. First, the claimed proteins are not used solely in basic research to study the proteins or their mechanism of action. Instead, the mutant Factor XI proteins can be used, and have been used, to identify inhibitors of Factor XI, which can themselves be used in a real world context, in particular, to treat thrombotic conditions. Second, the claimed mutant Factor XI proteins are not involved in the identification of inhibitors for treating an unspecified disease or condition; at least one inhibitor identified using the mutant Factor XI proteins, compound 22, has been shown to suppress thrombus formation *in vivo* in an acceptable animal model of the disease condition. Third, the inhibitors identified using the mutant Factor XI proteins have a specific, substantial, and

credible utility; they can be used to treat or prevent thrombotic conditions, as is taught by Applicants' specification. Fourth, and finally, the mutant Factor XI proteins, which are, arguably, intermediate products, are used to identify inhibitors of full-length Factor XI protein, which themselves have a specific, substantial, and credible utility (e.g., the treatment of thrombotic conditions), as is discussed above (*see, e.g., In re Kirk*, 376 F.2d 936, 945 (Fed. Cir. 1967); 153 U.S.P.Q. (BNA) 48; Intermediate products satisfy utility requirement when it can be shown that they produce a final product having a specific, substantial, and credible utility). Thus, contrary to the position taken by the Examiner, the mutant Factor XI proteins of present claims 102, 104, and 106-109 have more than simply a general utility; they have a specific, substantial, and credible utility.

The Examiner further suggests that Applicants' mutant Factor XI proteins are simply "research tools." The Examiner states that

> with regards to research tools, the MPEP states, "An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the invention is in fact 'useful' in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm..." MPEP § 2107.01(I). (Office Action, p. 5.)

As is clear from the discussion above, the claimed mutant Factor XI proteins demonstrate usefulness well beyond that found in a research setting. As is clear from Applicants disclosure, the mutant Factor XI proteins have been used to identify several inhibitors of full-length Factor XI, at least one of which, compound 22, has been shown to suppress thrombus formation *in vivo* in an acceptable animal model of the disease condition. Thus, Applicants' disclosure clearly demonstrates that the mutant Factor XI proteins of present claims 102, 104, and 106-109 exhibit a specific, substantial, and credible utility

well beyond that of a research tool. On this basis as well, the rejection of claims 102, 104, and 106-109 for lack of utility should be withdrawn.

Summary

The evidence provided by Applicants' specification clearly shows that mutant Factor XI proteins can be and have been used to identify compounds capable of inhibiting full-length Factor XI, which compounds can then be used in the treatment of thrombotic conditions (i.e., a real world context). It is Applicants' understanding that this assertion of utility is specific, substantial, and credible. Thus, for the rejection to stand, the Examiner must provide a rebuttal to Applicants' assertion of utility showing that the asserted utility is incredible. Applicants submit that the Examiner has failed to meet this burden. Accordingly, Applicants respectfully submit that the related rejections under 35 U.S.C. § 101 and § 112, first paragraph, for lack of utility and enablement should be withdrawn.

Rejections under 35 U.S.C. § 112, first paragraph

Written Description

Claims 104-109 are also rejected under 35 U.S.C. § 112, first paragraph, for lack of written description. The Examiner states:

> In the instant case, the claims are drawn to a myriad of mutant Factor XI proteins or fragments, wherein the mutation is a) a mutation of a residue that disrupts post-translational N-linked glycosylation, b) a mutation that eliminates a free, reactive sulfhydryl group of a cysteine, or c) an N- or C-terminal residue mutation that promotes crystallization relative to the native (nonmutated)...The specific structure of FXI is not described in the claims...The specification lacks sufficient description of all mutations

> which would have the asserted function, and does not provide sufficient variance in the genus to fully describe the myriad of mutations and fragments with mutations wihich are embraced by the generic. (Office Action, pp. 5-10.)

Applicants have cancelled claims 105 and have amended claims 102, 104, and 106-108, which are now directed to Factor XI proteins that include amino acids 370-607 as set forth in SEQ ID NO: 15 (i.e., the claims no longer recite unspecified "fragments" of Factor XI) and one or more of the recited mutations, and claim 109, which has been amended to recite a Factor XI protein that includes amino acids 370-605 (i.e., it lacks the C-terminal alanine and valine residues at positions 606 and 607 of the mature human Factor XI polypeptide sequence). The Examiner takes the position that the specification lacks a sufficient description of the myriad number of mutations that fall within present claims 104 and 106-109. In particular, the Examiner states that the full breadth of mutant Factor XI proteins covered by claim 104 are not described in Applicants' specification (i.e., Factor XI proteins having mutations that disrupt post-translational N-linked glycosylation, mutations that eliminate a free, reactive sulfhydryl group of a cysteine residue present in the protein, and mutations of the NH_2- or COOH-terminal residue of the protein that promote crystallization of the protein relative to wild-type Factor XI lacking the mutation). As was discussed in detail in the previous Reply to Office Action filed on February 6, 2006, each of these embodiments is described in considerable detail in the present specification.

M.P.E.P. § 2163 states that "[t]o satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one

skilled in the art can reasonably conclude that the inventor had possession of the claimed invention" (M.P.E.P. § 2163). In addition, the M.P.E.P. § 2164.05(a) states:

> The specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).

In support of the written description rejection, the Examiner states that the "level of skill and knowledge in the art...are low with respect to the effect of knowing what effect substitutions have on proteins" (Office Action, p. 7). Applicants remind the Examiner that the issue here is written description (i.e., whether possession of the invention can be demonstrated based on a description of the substitutions recited in the present claims), and not enablement[1] (i.e., whether undue experimentation would be required to determine the effect the substitutions recited in present claims 104 and 106-109 would have on the structure and function of the recited protein). Thus, the real issue is not whether one skilled in the art could predict the effect of the substitutions recited in present claim 104 on Factor XI protein based on the disclosure in Applicants' specification, but whether Applicants' specification describes the mutations recited in present claim 104 with sufficient detail to satisfy the written description requirement. Applicants submit that this burden has been met.

With the question properly framed, Applicants note that the level of skill in the art is high with respect to the practice of site-directed mutagenesis (i.e., the production of

[1] Applicants note that the claims do not require that the mutant Factor XI protein demonstrate any particular

mutant proteins, e.g., the mutant Factor XI proteins of present claims 104 and 106-109), specifically including such techniques as the removal of glycosylation sites, cysteine residues, and C- or N-terminal sequences, even in cases when the mutation affects the structure and function of the protein. Thus, Applicants' specification need not disclose each and every mutant Factor XI protein that falls within the scope of present claim 104 to satisfy the written description requirement because making such mutants is not new or non-conventional in the art (see MPEP § 2164.05(a), *supra*). In addition, MPEP § 2163(II)(A)(3)(a)(ii) states:

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice (see i)(A), above), reduction to drawings (see i)(B), above), or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus (see i)(C), above). (Citations omitted.)

Thus, a written description of a representative number of species within the genus by disclosure of relevant, identifying characteristics, e.g., structure, will suffice. As was clearly demonstrated in the last Reply to Office Action filed on February 6, 2006, and as is discussed in more detail below, Applicants' specification has provided a written description of a representative number of species within the genus of mutant Factor XI proteins recited in present claim 104.

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confirmation or function.

Factor XI Glycosylation Mutants

At the time the present application was filed, the skilled artisan knew that asparagine residues are post-translationally glycosylated when present within a known glycosylation consensus epitope, the sequence of which is defined as Asn-Xaa-(Ser/Thr), where Xaa is any amino acid except Pro. The specification teaches that one can alter the "residues in the consensus epitope for N-linked glycosylation...[such that] the protein would not be glycosylated" (see, e.g., page 83, lines 20-22, of the specification). Furthermore, it was also known that human Factor XI is glycosylated at one of five asparagine residues located within the mature Factor XI protein, e.g., at positions 72, 108, 335, 432, and 473 corresponding to human Factor XI; three of these positions fall within the sequence now recited in present claim 104. The specification teaches that a mutation at one or more of these residues produces a mutant Factor XI protein with reduced glycosylation. Because it was known that there are only a discreet number of glycosylation sites within wild-type Factor XI that are available for mutation, Applicants submit that possession of the claimed genus of Factor XI glycosylation mutants has been demonstrated. Thus, the specification clearly provides considerable written description with respect to mutations in Factor XI proteins that disrupt N-linked glycosylation.

Factor XI Cysteine Mutants

The specification also provides more than sufficient written description for mutant Factor XI proteins lacking a free, reactive sulfhydryl group of a cysteine residue. Applicants' specification teaches:

> The presence of free sulfhydryl groups on FXIcat monomers may also influence solubility, aggregation, and crystallization properties. For example, FXIcat has a single cysteine residue (Cys482) that is not involved in a disulfide bond. Cys482 forms a disulfide bond with Cys362 in intact Factor XI and thus is unpaired in the FXIcat. Thus, FXIcat-C482S was generated to replace the free sulfhydryl group with an isosteric serine residue. (Specification, p. 84, line 28, through page 85, line 5.)

Thus, Applicants' specification clearly discloses that unpaired cysteine residues can be eliminated from Factor XI proteins to produce the recited mutant Factor XI protein lacking a free, reactive sulfhydryl group of a cysteine residue. Because it was known that there are only a discreet number of cysteine residues within wild-type Factor XI that are available for mutation, Applicants submit that possession of the claimed genus of Factor XI cysteine mutants has also been demonstrated.

Factor XI NH_2- or COOH-Terminal Mutants

Finally, Applicants' specification also discloses that mutations in the amino- and carboxyl-terminal residues of the Factor XI protein can be prepared. Claim 104 recites that these mutations promote crystallization of the mutant Factor XI protein relative to the crystallization of wild-type Factor XI that lacks the mutation. Thus, preferred mutations are those that increase solubility, aggregation, and crystallization properties of the mutant Factor XI protein. Given the teachings in Applicants' specification, such determinations can be easily made by one who practices in the field of crystallography. Accordingly, Applicants submit that possession of the genus of Factor XI amino- or carboxyl-terminal mutants has also been demonstrated. Applicants also note that biological activity of the

mutant Factor XI protein has not been claimed. Thus, the mutant Factor XI proteins need not demonstrate biological activity.

In summary, Applicants' specification provides a description of mutant Factor XI proteins that is more than sufficient to satisfy the written description requirement with respect to present claims 104 and 106-109. Contrary to the Examiner's position, a written description of all of the myriad mutant Factor XI proteins thereof is not required. For the purposes of written description, all that is required is that Applicants' specification describe the claimed invention in sufficient detail such that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention (M.P.E.P. § 2163). Applicants have clearly satisfied this burden. For all the reasons discussed above, Applicants respectfully request withdrawal of the rejection of claims 104-109 under 35 U.S.C. § 112, first paragraph, for lack of written description.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 105, 107, and 108 are rejected under 35 U.S.C. § 112, second paragraph, for indefiniteness. The Examiner states that claim 105 recites "'a human polypeptide sequence'...[but] [i]t is unclear what constitutes 'a human polypeptide sequence', as compared to, e.g., a synthetic peptide" (Office Action, p. 10). Applicants have cancelled claim 105. This rejection can be withdrawn.

The Examiner rejects claims 107 and 108, stating:

> it is unclear whether the protein or fragment of claims 104 (and/or 106) must be SEQ ID NO:15, or whether it can be any peptide so long as it has some amino acid which corresponds to said single point mutation(s). In the latter case, the claim is indefinite because one would not be able to

determine what peptides are, or are not, embraced by the claims. (Office Action, pp.10-11.)

Applicants have amended present claim 104 to recite that the Factor XI protein includes amino acids 370-607 of SEQ ID NO: 15 and at least one of the additional mutations described in parts (a)-(c) of the claim. Thus, dependent claims 107 and 108 recite specific point mutants that fall within this defined amino acid sequence. For this reason, the metes and bounds of pending claims 104, 106, and 107-109 is not unclear. This rejection should be withdrawn.

Finally, the Examiner rejects claim 18 stating that "it is unclear whether the specific mutation required by claim 108 is C482S, or whether the amino acid position 482 is mutated from S482 to another amino acid" (Office Action, p. 11). Applicants have amended claim 108 to clarify that the protein contains a Cys to Ser point mutation at position 482, relative to the numbering set forth in SEQ ID NO: 15. Thus, the residue at this position is a serine and not another amino acid. This rejection should be withdrawn.

Rejections under 35 U.S.C. § 102

The Examiner rejects claims 104, 105, and 109 under 35 U.S.C. § 102(b) over Konishi; claims 104-106 and 109 under 35 U.S.C. § 102(b) over Schmid; claims 102, 104, 105, and 109 under 35 U.S.C. § 102(b) over Penning; claims 102, 104, 105, 107, and 109 under 35 U.S.C. § 102(b) over Strominger; and claims 104, 105, 108, and 109 under 35 U.S.C. § 102(e) over Wang. For each of these rejections, the Examiner states that the cited reference discloses a fragment of Factor XI, whether that fragment consists of one

amino acid (Strominger) or more (Konishi, Schmid, Penning, and Wang). Applicants have amended present independent claims 102 and 104, which now recite a purified human Factor XI protein that includes amino acids 370-607 as set forth in SEQ ID NO: 15 and at least one of the mutations specified in the claims. Because none of Konishi, Schmid, Penning, Strominger, or Wang teach or suggest the mutant Factor XI proteins recited in present claims 102, 104, and 106-109, the rejections under 35 U.S.C. § 102 should be withdrawn.

CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is requested.

Enclosed is a Petition to extend the period for replying for three months, to and including November 6, 2006, as November 4, 2006, fell on a Saturday, and a check in payment of the required extension fee. If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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